REMARKS

Upon entry of the above amendments, claims 12-39, 58-73 will be pending. Applicants reserve the right to pursue subject matter that will no longer be pending after the amendment above, or which has not yet been pursued, in a related application. The claim amendments add no new matter as there is basis in the specification throughout, for example, in the claims as filed.

Applicants respectfully request consideration of the pending claims.

Election/Restrictions

Applicants thank the Examiner for withdrawing the requirement for election of species issued in the previous Office Action entered December 12, 2005. Following the election of Group 1, claims 40-57 are cancelled without prejudice to further prosecution.

Claim Interpretation

The Examiner stated that the phrase "'determining sequence variations' in the claims is interpreted to mean discerning the actual sequence of the biomolecule in question, and not the mere determination that a sequence variation exists." This Response is consistent with the Examiner's interpretation of the phrase.

Claim Rejections – 35 USC Section 112- 2nd Paragraph

Claim 7 was rejected for providing insufficient antecedent basis for this limitation in the claim. Applicants thank the Examiner for pointing out this accidental error and note that claim 7 has been cancelled.

Claim Rejections – 35 USC Section 112 – Enablement

Claims 1-39 and 58-73 were rejected under 35 USC 112 first paragraph, because "the

specification, while being enabling for determining sequence variations in nucleic acids and proteins for which some prior knowledge of possible sequence variation exists, does not reasonably provide enablement for determining sequence variations in any biomolecule or in cases where no prior knowledge of sequence variations exists." Given that the presently pending claims refer to nucleic acid sequence variations, Applicants respectfully request that the Examiner withdraw the rejection of these claims. As to the Examiner's statement that the enablement is limited to only sequence variations in nucleic acids and proteins for which some prior knowledge of possible sequence variation exists Applicants respectfully disagree with the Examiner. Following the methods of the present invention, a target nucleic acid may be found to have a sequence variation by first finding a fragment that is different from the corresponding reference fragment. Using methods of sequencing known in the art, and referenced in the background section of the specification, one of ordinary skill in the art would then be able to determine a sequence variation, even if there was no prior knowledge of such a sequence variation. Applicants therefore respectfully request that the rejection of remaining pending claims 12-39 and 58-73 be withdrawn.

Claim Rejections – 35 USC Section 102

Claims 1, 2, 4-7, 9-11, 13-22, 24, 58, and 69-73 were rejected under 35 USC 102(b) as being anticipated by Zabeau et al (WO 00/66771). Claims 1, 2, 4-7, and 9-11 have been cancelled, claims 13-22, 24, and 58 have been amended to be directly or indirectly dependent on amended claim 12, and claims 69-73 are directly or indirectly dependent on amended claim 65, without prejudice to the omitted or deleted claim subject matter. With these amendments, these pending claims, 13-22, 24, 58, and 69-73 all include the steps of "determining compomers corresponding to the identified different fragments in step a) that are compomer witnesses; and determining a reduced set of sequence variations [or single nucleotide polymorphisms] corresponding to the compomer witnesses that are candidate sequences to determine the sequence variations in the target nucleic acid compared to the reference nucleic acid." Zabeau does not teach this limitation, as stated by the Examiner at pages 14-15 of the March 8 Office Action, therefore the pending claims are not anticipated by this reference. Applicants therefore respectfully request that the rejection of these claims be withdrawn.

Claims 1-3 were rejected under 35 USC 102(b) as being anticipated by Chait et al (USPN 6,271,037). As stated above, claims 1-3 were cancelled without prejudice to their further prosecution, therefore, this rejection is no longer relevant to any pending claim in this application.

Claim Rejections 35 USC Section 103

Claims 8, 12, 26-32, 34-39, and 59-64 were rejected under 35 USC 103(a) as being unpatentable over Zabeau et al.

The Examiner states that "Zabeau **does not teach**" the "limitation expressed in claims 8, 12, 29, 35 and 59 of, as stated in claim 8, determining compomers corresponding to the different fragments...that are compomer witnesses; and...determining a reduced set of sequence variation candidates corresponding to the compomer witnesses." Claim 8 has been cancelled, and the remaining pending claims following this Amendment all contain a limitation to determining compomers, a limitation that the Examiner states is not taught by Zabeau.

The Examiner then, however, refers to Zabeau at page 4, lines 18-20 as supporting the use of compomers, citing Zabeau at page 4, lines 18-20, and stating that "it would have been *prima facie* obvious...to modify the method of Zabeau to incorporate the optional step taught by Zabeau of determining the base composition to reduce the number of possible compositional isomers (i.e. compomers). But, it is important to note that the reference by Zabeau to compositional isomers is in the background section of the reference. The Examiner's citation is presented in context below:

> Some of the MS-based assays have been used for the scoring of defined mutations or polymorphisms. Other processes derive multiple oligonucleotide fragments and yield a "mass-fingerprint" so as to analyze a larger target nucleic acid region for mutation and/or polymorphism. The latter MS analyses are however considerably less informative in that they are essentially restricted to the detection of sequence variations. *The methods cannot be applied to diagnostic sequencing of nucleic acids, where the term diagnostic sequencing means the unequivocal determination of the presence, the nature and the position of sequence variations.* **At best, the measurements confirm the base composition of small fragments whose masses are determined with sufficient accuracy to reduce the number of possible compositional isomers**. Also, it will be realized that only certain changes in composition (as revealed by shifts in the mass spectrum) can be

> unambiguously assigned to a polymorphism or mutation. (Zabeau, page 4, ll. 10-22, cited lines 18-20 in bold, and emphasis added in italics).

Given that the reference to compositional isomers is in the background section of the Zabeau reference, and given the context in which these compositional isomers are presented, Applicants believe that the that Zabeau reference does not teach or suggest combining the "preferred embodiment" of Zabeau (as discussed by the Examiner) with the use of compositional isomers. Although the Examiner states that one of skill in the art "would have been motivated [to combine the two teachings] in cases where known polymorphisms were being assessed, because this would require fewer cleavage reactions," Applicants do not believe that Zabeau provides any motivation to do so. Instead, the use of compositional isomers is only referred to as relevant to prior art methods, and there is no teaching of any need to seek out fewer cleavage reactions. Applicants do not believe that Zabeau teaches that what he refers to as a background state of the art relating to compositional isomers should be combined with Zabeau's description of its method. Without any motivation to combine these two teachings, Applicants do not believe that there is a prima facie case of obviousness.

Further, Zabeau states that these prior art MS analyses cannot be applied to diagnostic sequencing because they do not unequivocally determine "the presence, the nature and the position of sequence variations," and "at best" only reduce the number of possible compositional isomers. The present invention, in contrast, does provide methods involving the use of compositional isomers to reduce the number of sequence variations to analyze; these methods do result in the determination of the presence, nature, and position of sequence variations. In this passage, however, Zabeau characterizes methods that "at best" reduce the number of compositional isomers as not being sufficient to determine the presence, the nature and the position of sequence variations." Thus, one of ordinary skill in the art would have no motivation to combine Zabeau's method with a method for reducing the number of possible compositional isomers.

Applicants therefore respectfully request that the presently pending claims be found nonobvious over Zabeau.

Double-Patenting

Claims 1-39 and 58-73 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-42 of copending Application No. 10/933,611. As this rejection is a provisional rejection, Applicants will await the notice that one of the sets of claims is allowable, and will file any terminal disclaimer, if appropriate, at that time.

CONCLUSION

Applicants respectfully submit that, after entry of the amendment above, all pending claims will be in condition for allowance, and they earnestly solicit an early notice to such effect. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (760) 473-9472 so that they may be promptly resolved.

Respectfully submitted,

Dated: 8 September 2006 By: _____

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